

## Rezulin

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### Press Accounts

## Death Toll Challenges Rezulin Safety Claim

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Los Angeles Times

By David Willman

*Medicine: Fatalities climb despite drug maker's assurances. FDA to reassess approval.*

WASHINGTON—It was a bold claim. On Dec. 31, the Warner-Lambert Co. assured the federal government that liver-related deaths linked to Rezulin, its controversial drug for adult-onset diabetes, had declined dramatically from the previous year.

The company, with sales of Rezulin topping \$ 1 billion, also distributed the claim to doctors and on the Internet.

But medical reports collected by Warner-Lambert and the Food and Drug Administration tell a different story.

Reports of liver-related fatalities in which Rezulin was cited as a contributing factor have more than quadrupled, from 14 in 1997 to 65 in 1998, according to newly obtained federal records. An additional 12 liver-related deaths were reported in the first six weeks of this year.

Including the liver-related cases, the deaths of 155 Rezulin patients have been reported since the drug went on the market in March 1997, the records show. About 60% of the 155 patients showed signs of liver damage.

The higher figures have come to light as the FDA is reconsidering its 1996 approval of Rezulin. The same advisory panel that unanimously endorsed the drug will consider formally whether to recommend banning or restricting it at a March 26 meeting in Bethesda, Md.

The agency's unusual action follows a Los Angeles Times series, published Dec. 67, reporting that the FDA had dismissed explicit warnings of danger while racing to grant "fast-track" approval of Rezulin.

Nearly all of the 155 deaths were reported to the FDA and Warner-Lambert by doctors, nurses, pharmacists and other health-care professionals who listed Rezulin as a "suspect" drug. These records--among thousands of adverse drug reaction reports on Rezulin--were obtained last month from the FDA through the Freedom of Information Act and analyzed as part of a Times computer-assisted study.

The number of Rezulin-related deaths cited in the new records is more than five times higher than the 26 that Warner-Lambert acknowledged through Nov. 30.

Warner-Lambert apparently excluded most of the Rezulin-related deaths reported by health professionals. The company has not divulged the methodology or criteria used to reach its conclusions.

#### Company Cites Drug's 'Important Role'

Company officials insist that Rezulin is safe when used with regular liver-function monitoring and that the drug's risks should be weighed against its benefits and the serious complications that can arise from diabetes.

A Warner-Lambert representative said last week that the company would not comment on Rezulin deaths before the FDA advisory committee meeting.

"We remain confident that a scientific, objective evaluation of the data by the advisory committee will reconfirm the important role of Rezulin" in treating adult-onset diabetes, said the spokeswoman, Carol Goodrich.

But the FDA, in a previously undisclosed letter to Rep. Henry A. Waxman (D-Los Angeles), said that as of Feb. 3 it was aware of 100 Rezulin patients who suffered "liver adverse events with a fatal outcome." The agency described 33 of these deaths as "associated" with the use of Rezulin. In addition, the FDA identified 738 other possible cases of serious "adverse reactions" involving Rezulin, including disability, "life-threatening" injuries and hospitalization.

FDA spokesman Larry Bachorik this week declined to describe the basis upon which the agency excluded 67 of the 100 deaths. "The number is subject to change," Bachorik said, adding that the agency will present revised findings at the March 26 review.

Among the 155 fatalities counted by the Times study, some of the patients also had other preexisting medical conditions that could have contributed to or caused their deaths, according to the reports. The liver-related signs that appear on the death reports include laboratory evidence of injury or specific clinical findings, such as hepatitis or jaundice.

Although Rezulin was on the market for nine months in 1997 compared to all of 1998, the company has said that roughly the same number of patients--705,000--began taking the drug during each of the two years.

Rezulin has been extolled by some doctors as a "miracle" pill for the 15 million Americans who suffer from adult-onset diabetes. On the market since March 1997, it is one of 10 or more medications that helps control blood-sugar levels.

The company originally promoted Rezulin as a once-a-day pill that would allow some adult-onset, "Type 2" diabetics to halt insulin injections. People with Type 2 diabetes have elevated blood-sugar levels, even though their bodies typically produce insulin, the hormone that lowers blood sugar. (Juvenile-onset, "Type 1" diabetics cannot produce their own insulin and would die without daily injections.)

Some physicians continue to believe that Rezulin's benefits outweigh its risks. Others have become so concerned that they are no longer waiting for the FDA review.

For example, some diabetes specialists at the prestigious Mayo Clinic in Rochester, Minn., have ceased recommending Rezulin to their patients.

"People are holding off on prescribing the drug until we have a better handle on its safety," said Dr. Sean F. Dinneen, an endocrinologist at the Mayo Clinic.

## 'We're Going to See More Deaths'

Dr. Srini R. Vasa, a liver specialist at the University of Kansas Medical Center, said: "When I see any patient on this drug, I'm really, really uneasy."

Two patients who came under Vasa's care died after taking Rezulin. In a third case, Vasa oversaw a successful liver transplant in January for a 53-year-old Kansas City, Kan., woman. She suffered liver failure only weeks after starting on Rezulin.

"We're going to see more deaths," Vasa said. "We don't have to wait for another 100, 200 patients to be transplanted before we start taking this drug off the market ."

The Times study found that 91 of the 155 total deaths reported to the FDA since 1997 involved signs of liver damage--a marker that is consistent with Rezulin's demonstrated capacity to damage this vital organ.

The growing toll of liver-related fatalities reported among Rezulin users clashes with the sweeping safety claims made by Warner-Lambert, a major U.S. pharmaceutical firm and maker of consumer products.

In mid-December a Warner-Lambert vice president, Stephen J. Mock, said in an interview that he was not aware of a single Rezulin-related death since July, when the company and the FDA issued a third, stricter set of liver-monitoring recommendations.

"The reported events relating to . . . deaths or liver transplants since the label was changed July 28 is zero," Mock said.

In fact, Warner-Lambert had reported 31 deaths to the FDA from July 28 to Dec. 17, FDA records show.

In its Dec. 31 submission to the FDA, Warner-Lambert stated: "The number of deaths in patients initiating Rezulin therapy in 1998 is approximately 65% lower than the number for patients initiating therapy in 1997."

The company also claimed in the FDA filing that liver-monitoring precautions have "substantially" reduced the pace of adverse reactions, including deaths.

## Company Was Aware of Most Deaths

The Times analyzed 2,971 adverse drug reaction reports filed between March 27, 1997, soon after Rezulin was introduced, and Feb. 9, 1999, the most recent date for which records were available. The study was directed by Thomas J. Moore, a fellow in health policy at George Washington University Medical Center. The methodology and results were reviewed by Sheila R. Weiss, a former FDA epidemiologist who is an assistant professor at the University of Maryland's Department of Pharmacy Practice and Science.

The study found that:

Warner-Lambert was aware of most of the deaths since the drug went on the market two years ago. In 129 of the cases, the events were reported directly to the FDA by the company.

The number of reported deaths did not drop following the latest change to the liver-monitoring recommendations. There have been 57 Rezulin-related fatalities since last July 28, compared to 55 in the previous six months.

Nearly 60% of all the reported deaths involved liver problems. This high incidence supports early evidence of liver toxicity seen during clinical testing of Rezulin.

Of the 155 victims, ages ranged from 17 to 91 years old; 61% were women and 39% were men; 138 of

the deaths occurred in the United States.

For about 4 of 10 victims, Rezulin was the only diabetes treatment cited. Other patients used the drug in combination with insulin or other medications.

As part of its review, the FDA is reevaluating the safety and effectiveness of the drug when it is taken by itself to treat adult-onset diabetes.

#### Stand-Alone Use Draws Criticism

The use of Rezulin as a standalone "monotherapy" has been a cornerstone of Warner-Lambert's aggressive marketing efforts. In full-page magazine and newspaper ads, the company has touted Rezulin as a once-a-day pill for treating adult-onset diabetes.

But many patients do not respond to the drug when taken by itself. Indeed, an FDA medical officer, Dr. Robert I. Misbin, wrote last month in *Annals of Internal Medicine* that those patients are "needlessly exposed to the potential hazard of liver damage" if they have failed to improve within the first two months on the drug. In 1997, Misbin backed Rezulin's approval.

The death reports identified in the Times study came from two separate computer systems used by the FDA during the last 18 months, a changeover that made it more difficult for the agency to track its own data. In many instances, multiple reports of the same death were filed by health professionals. These duplicates were culled by the Times study through repeated checks with the assistance of a computer and by hand.

When the FDA granted "fast-track" approval to Rezulin two years ago, little was said publicly about the drug's risks. The Times series in December disclosed that a veteran FDA medical officer with expertise in diabetes medications was stripped of his assignment to examine Rezulin after recommending its rejection. Dr. John L. Gueriguian said he based his opposition in part on the drug's potential liver toxicity and its dubious possible benefits.

Rezulin was withdrawn from the market in Britain in December 1997 because of concerns about liver toxicity.

#### Many More Deaths Are Suspected

The FDA typically weighs the risks and benefits of a potentially dangerous drug before deciding whether to pull it from the U.S. market. Last year, for example, the pain killer Duract was removed after its use was linked to four liver-failure deaths.

And even now, the 155 reported deaths are only a fraction of the likely total fatalities during Rezulin's first two years on the market. This is because doctors, hospitals and others in the U.S. health-care system are not required by law to report deaths or other problems related to the use of any prescription drug.

"You can be sure that the deaths reported for Rezulin are a tiny proportion of the total," said Dr. Brian L. Strom, chairman of biostatistics and epidemiology at the University of Pennsylvania School of Medicine.

Despite the safety controversy, Warner-Lambert is asking the FDA at next week's meeting not only to keep Rezulin on the market but to allow even broader use of the drug--in combination with a popular competitor, called Glucophage.

Dr. G. Alexander Fleming, a former senior FDA medical officer who supported the original approval of Rezulin before soon developing his own doubts, noted the company's unyielding posture.

"This company's really got chutzpah," Fleming said.

#### Death Count

A breakdown of the reported deaths associated with Rezulin.

By age group

Under 50: 12

50-59: 24

60-69: 48

70-79: 33

80 and older: 17

Note: Some victims' ages were not provided

By year

1st six weeks: 20 deaths

Note: Rezulin on the market for nine months in 1997.

Source: Times analysis of FDA records

Times staff writers Judy Lin and Heidi Sherman and researcher Tricia Ford in Washington and researcher Janet Lundblad in Los Angeles contributed to this story.